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Date January 10, 2011

To Examiner Lakshmi S. Channavajjala

Of USPTO

Fax (571) 273-0591

From Sunhee Lee and Jerrick J. Ho

Atty Docket No. Q64175 U.S. Appl. No. 09/848,225

Pages 25  
(including cover sheet)

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Examiner Channavajjala,

Thank you for discussing the above-identified application with us today. In response to your request, please find the translations of JP 4-193814 and JP 63-192703, presented in the interview, attached for your reference.

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## STATEMENT

I, Satoshi OHGUSHI—hereby declare that I am conversant in both Japanese and English languages and that I believe the following is a true and correct translation of JP 4-193814 A.

Date: January 7, 2011

A handwritten signature in cursive script, reading "Satoshi Ohgushi".

Satoshi OHGUSHI

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		A 61 K 7/00	V	9051-4C
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10 Request for Examination: not made

Number of Claim: 1 (6 pages in total)

(54) Title of the Invention: Transparent or semi-transparent cosmetic composition

(21) Application Number: Hei-2-322081

(22) Application Date: November 26, 1990

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## Specification

### 1. Title of the Invention

Transparent or semi-transparent cosmetic composition

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### 2. Claims

(1) A cosmetic composition comprising:

(A) 0.05-30% by weight of an amphipathic lipid,

(B) 0.05-30% by weight of a nonionic surfactant,

10 (C) 1-50% by weight, based on (B), of an ionic surfactant, and

(D) 40-99% by weight of an aqueous medium,

wherein said composition is transparent or semi-transparent, and wherein the ratio of (A)/[(B)+(C)] is 0.2-10.

### 15 3. Detailed Description of the Invention

[Industrial Field of Application]

This invention relates to a cosmetic composition in which amphiphatic lipids are stably microdispersed in an aqueous medium, and which exhibits a transparent or semitransparent appearance.

20

[Background Art and Problems that the Invention is to Solve]

The water content of the stratum corneum decreases as the skin becomes more rough, dry, or aged. It is believed that oils increase the water content of the stratum corneum by occlusion of the skin surface or by directly acting on the stratum corneum, thereby softening the stratum corneum. On the other hand, it is believed that aqueous moisture retaining agents increase the water content of the stratum corneum because of

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their water retaining ability, resulting in a softening of the stratum corneum. This is why cosmetic compositions containing various oils or aqueous moisture retaining agents, improve the feel of the skin and the skin's appearance.

However, oils have the problem that they tend to be greasy or cause a skin shine. Aqueous moisture retaining agents are likely to be washed away with water, resulting in a short-lived cosmetic effect.

Amphipathic lipids such as intercellular lipids, extracted from the skin, have been used in cosmetic compositions instead of oils or aqueous moisturizing agents, (JP 62-29508 A, JP 62-120308 A). Likewise synthetic compounds having analogous structures to intercellular lipids have also been used for similar purposes (JP 62-228048 A). Intercellular lipids, are found in the intercellular portions of the stratum corneum, and form stratified structures which aid in the adhesion of the stratum corneum cells, and in the hydration of the stratum corneum. Amphipathic lipids, such as the intercellular lipids, are solid at room temperature (25°C), and are incorporated into the cosmetic composition with the emulsified state by mixing with oils, or with dissolved state by using large amounts of surfactant when used in a stable state in cosmetics.

Only opaque, white emulsions are obtained by these methods other than the method in which large amounts of surfactant is used, and it is difficult to incorporate intercellular lipids stably into cosmetic compositions wherein the lipids are in high concentration. In addition, large amounts of surfactant, tends to interfere with the function of the amphipathic lipids, sometimes resulting in skin irritation due to the surfactants.

It would be desirable, therefore, to provide a cosmetic composition which does not irritate the skin, but which contains the amphipathic lipids in a stable and clear transparent or semi-transparent condition.

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[Means for Solving the Problems]

Under such a situation, the present inventor diligently made investigations. As a result, it has been found that, by the use of a nonionic surfactant in combination with an ionic surfactant, the appearance of the resulting cosmetic composition is beautifully  
5 transparent or semi-transparent, and the amphiphatic lipids which are stable and microdispersed can be incorporated therein with relatively small quantity of the surfactant.

Specifically, a cosmetic composition has been provided which comprises:

- (A) 0.05-30% by weight of an amphiphatic lipid,
- 10 (B) 0.05-30% by weight of a nonionic surfactant,
- (C) 1-50% by weight, based on (b), of an ionic surfactant, and
- (D) 40-99% by weight of an aqueous medium,

wherein said composition is transparent or semi-transparent, and wherein the ratio of (A)/[(B)+(C)] is 0.2-10.

15 In this invention, the cosmetic composition which has about 1-1500 ppm of turbidity is referred to as transparent or semi-transparent. Turbidity is measured using purified Kaolin as a standard in aqueous solution (1 ng/liter) of 1 ppm as measured by a Turbidimeter

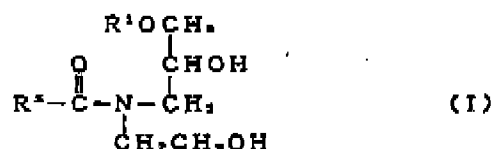
An amphiphatic lipid (A) of this invention is defined as a lipid which has both  
20 hydrophobic group(s) and hydrophilic group(s) and can be dispersed in water but is not water soluble, and which is solid at room temperature (25°C). Suitable amphiphatic lipids include the higher alcohols, fatty acids, ceramides, glycoceramides, phospholipids, glycolipids, cholesterol, cholesterol fatty acid esters, and derivatives thereof.

25 Preferred are the amphiphatic lipids of the formula (I)

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wherein  $\text{R}^1$  is a straight-chain or branched, saturated or unsaturated hydrocarbon having 10 to 26 carbon atoms, and  $\text{R}^2$  is a straight-chain or branched, saturated or unsaturated hydrocarbon having 9 to 25 carbon atoms.

5           The method of preparation of the compound presented by formula (I) is described in JP 62-228048 A, JP 63-216852 A. The amphiphatic lipids described above can be used individually or in combination. The amide derivative (I) is especially preferably used individually or in combination with the other amphiphatic lipids. When the combination of amide derivative (I) and another amphiphatic lipid is used, it is  
10       preferable that the ratio be in the range of 100/1-1/100, and more preferably 10/1-1/10. Amphiphatic compounds are incorporated in the present cosmetic composition in an amount of 0.05-30% by weight, preferably 0.1-10% by weight based on the total composition.

Suitable nonionic surfactants (B) for use in the present composition include,  
15       surfactants with polyoxyethylene, for example, polyoxyethylene hydrogenated castor oil; polyoxyethylene sorbitan fatty acid ester, such as polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan tetraoleate; polyoxyethylene glyceryl fatty acid ester, such as polyoxyethylene glyceryl monoisostearate, polyoxyethylene glyceryl triisostearate; polyethylene glycol fatty acid ester, such as polyethylene glycol  
20       monoisostearate; polyoxyethylene alkyl ether, such as polyoxyethylene hexyl decyl ether, polyoxyethylene octyl dodecyl ether, polyoxyethylene lauryl ether, polyoxyethylene cetyl ether, polyoxyethylene stearyl ether, polyoxyethylene oleyl ether, polyoxyethylene nonyl phenyl ether. Other nonionic surfactants, such as polyglycerine alkyl ether, polyglycerine fatty acid ester, sucrose fatty acid ester are also usable.  
25       Preferred nonionic surfactants are polyoxyethylene hydrogenated castor oil or a

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polyoxyethylene alkyl ether having HLB 8 to 20, preferably 10-16. These nonionic surfactants may be used individually or in combination, so long as the total has an HLB of 8 to 20. The cosmetic composition of this invention contains 0.05-30% by weight, preferably 0.1-10% by weight of the component (B) based on the total composition.

5           Ionic surfactant(s) used in this invention are anionic surfactants, amphoteric surfactants or cationic surfactants. Suitable anionic surfactants for use in the present composition include polyoxyethylene alkyl sulphate, such as sodium polyoxyethylene lauryl ether sulphate, polyoxyethylene lauryl ether sulphate triethanol amine; N-acyl amino acids such as sodium lauroyl sarcocin, sodium lauroyl methylalanine;

10       polyoxyethylene alkyl ether phosphates, such as sodium polyoxyethylene lauryl ether phosphate, sodium polyoxyethylene cetyl ether phosphate, dipolyoxyethylene alkyl ether phosphates, tripolyoxyethylene alkyl ether phosphates, dipolyoxyethylene phenyl ether phosphates, sodium polyoxyethylene lauryl ether phosphate, sodium

15       dipolyoxyethylene lauryl ether phosphates. Suitable amphoteric surfactants for use in the present composition include alkylbetaine, alkylaminobetaine, alkylsulphobetaine. Suitable cationic surfactants for use in the present composition include the di-long chain alkyl quaternary ammonium salt, mono-long chain alkyl quaternary ammonium salt, di-long chain alkyl polyoxyethylene quaternary ammonium salts, mono-long chain alkyl polyoxyethylene quaternary ammonium salts, bis-(hydroxyalkyl) quaternary ammonium

20       salt, quaternary ammonium salts having an amide bond or ester bond. These can be used alone or in combination. Component (C) is used in an amount of 1-50% by weight, preferably 2-30% by weight based on the weight of component (B). If the amount of the component (C) is out of this range, the cosmetic composition will not be adequately transparent or semi-transparent.

25           Components (A), (B), and (C) are incorporated in the cosmetic composition in the ratio of  $(A)/[(B)+(C)]=0.2-10$ , preferably 0.5-2. If the ratio of  $(A)/[(B)+(C)]$  is less



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than 0.2, the relative amount of surfactant will be so large that the composition may become transparent, but the irritation to the skin will be a potential problem. If the ratio of (A)/[(B)+(C)] is larger than 10, the composition will not be adequately transparent or semi-transparent.

5           Suitable aqueous medium (D) for use in the present composition include water, or a combination of water and an aqueous alcohol, such as ethanol, glycerine, sorbitol, propyleneglycol, dipropyleneglycol, 1,3-butanediol. Component (D) is used in an amount of 40-99% by weight, preferably 80-95% by weight, based on the total composition.

10           Other than the above, ingredients as usually present in cosmetics may be present here as well, including oils, silicone oils, polyols, water soluble polymers, UV-ray absorbers, antiseptics, perfumes, ethanol, inorganic or organic powders, germicides, colorants and the like. It is preferred that oil not be used in the present composition. The maximum should be about 2% by weight even if incorporated.

15           While the cosmetic composition of this invention is beautifully transparent or semi-transparent, a latex or other reagent can be added to increase the turbidity, if desired. It is also possible to incorporate an ethyleneglycol ester to obtain pearl-like product.

          The composition of this invention is produced as follows: Components (A), (B)  
20   and (C) are mixed and melted at high temperatures of 65°C-95°C and then aqueous separately mixed is added thereto. An anisotropic liquid crystal phase is formed, and then a lipid microdispersion is obtained. By cooling this to room temperature, the cosmetic composition of the present invention is produced.

          In this process, it is preferable that polyols such as glycerine be incorporated  
25   into the lipids and surfactants phase, to produce effectively the lipid microdispersion system.

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## [Examples]

The present invention will be described in detail by way of the following examples. The present invention, however, is not limited to these examples.

5

## Examples 1-28

The components except water, in the Table 1 to 3, were mixed and melted at a temperature of 85°C-90°C. Hot water heated to the same temperature was added, and the composition was cooled to room temperature to produce a lotion. All of the lotion

10 obtained was transparent or semi-transparent.

TABLE 1

	Examples											
	1	2	3	4	5	6	7	8	9	10	11	12
Polyoxyethylene hydrogenated castor oil												
(5E.O)					0.33							
(10E.O)				1.39		0.83						
(20E.O)							0.89					
(30E.O)	2.5						0.89	1.00				
(40E.O)		2.5							1.7	2.1	3.75	2.5
(50E.O)			2.5		2.17	1.47	1.61	1.50				
(60E.O)				1.11								
Sodium polyoxyethylene lauryl ether phosphate (4E.O)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.4	0.25	0.5
Amide derivative R <sup>1</sup> = C <sub>16</sub> H <sub>33</sub> , R <sup>2</sup> = C <sub>12</sub> H <sub>25</sub>	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	1.45
Antiseptics	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
96% Glycerin	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Water	bal.	bal.	bal.	bal.	bal.	bal.	bal.	bal.	bal.	bal.	bal.	bal.

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TABLE 2

	Examples							
	13	14	15	16	17	18	19	20
Polyoxyethylene hydrogenated castor oil (40E.O)	2.5							
Polyoxyethylene lauryl ether (9E.O)				0.5				
Polyoxyethylene lauryl ether (23E.O)			2.5	0.5				
Polyoxyethylene isocetyl ether (20E.O)		2.5		1.5				
Polyoxyethylene cetyl ether (13E.O)					2.5			
Polyoxyethylene stearyl ether (12E.O)						2.5		
Polyoxyethylene oleyl ether (13E.O)			2.5				2.5	
Polyoxyethylene monoisostearate (14E.O)								2.5
Sodium polyoxyethylene lauryl ether phosphate (4E.O)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Amide derivative [ $R^1 = C_{16}H_{33}$ , $R^2 = C_{15}H_{31}$ ]	1.8	1.6	1.6	1.6	1.6	1.6	1.6	3.0
Squalene		1.4	1.4	1.4	1.4	1.4	1.4	
Cetanol	0.72							
Stearyl alcohol	0.48							
86% Glycerin	7.0	5.5	5.5	5.5	5.5	5.5	5.5	3.0
55% Ethanol		20.0	20.0	20.0	20.0	20.0	20.0	20.0
Water	bal.	bal.	bal.	bal.	bal.	bal.	bal.	bal.

TABLE 3

	Examples							
	21	22	23	24	25	26	27	28
Polyoxyethylene hydrogenated castor oil (40E.O)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium polyoxyethylene lauryl ether phosphate (4E.O)	0.1	0.3						0.3
Sodium polyoxyethylene cetyl ether phosphate (5E.O)			0.5					
Dipolyoxyethylene alkyl ether phosphate (4E.O)								0.2
Sodium polyoxyethylene lauryl ether sulphate				0.5				
Polyoxyethylene lauryl ether sulphate triethanol amine					0.5			
Sodium lauroyl sarcocin						0.5		
Sodium lauroyl methylalanine							0.5	
Amide derivative [ $R^1 = C_{16}H_{33}$ , $R^2 = C_9H_{19}$ ]	1.65	1.65	1.65	1.65	1.65	1.65	1.65	1.65
Cholesterol	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
Stearic acid	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33
Palmitic acid	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27
Cholesteryl isostearate	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
86% Glycerin	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Water	bal.	bal.	bal.	bal.	bal.	bal.	bal.	bal.

## 5 [Advantage of the Invention]

As described above, the amphipathic lipids is stably incorporated with high concentration into the cosmetic composition of the present invention, and the appearance of the cosmetic composition is beautifully transparent or semi-transparent

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## STATEMENT

I, Satoshi OHGUSHI—hereby declare that I am conversant in both Japanese and English languages and that I believe the following is a true and correct translation of JP-A-63-192703.

Date: December 29, 2010



Satoshi OHGUSHI

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# 4/ 16

(19) Japanese Patent Office (JP)

(12) Publication of Patent Application

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(43) Date of publication: August 10, 1988

5 (51) Int. Cl<sup>4</sup>: A61K 7/00, 7/48

Identification Number

Intraoffice Reference Number: 7306-4C, 6971-4C

Request for Examination: made

Number of Claims: 1 (8 pages in total)

10 (54) Title of the Invention: External Agent for Skin

(21) Application Number: Sho-62-24391

(22) Application Date: February 4, 1987

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(72) Agent: Patent Attorney Mitsuyuki Ariga, and two others

20

## Specification

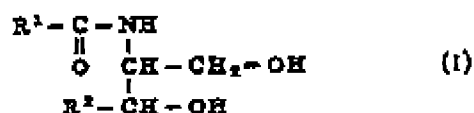
## 1. Title of the Invention

External Agent for Skin

## 2. Claim

25 1. An external agent for skin, which comprises the following components (A) and (B),

(A) one or two or more of ceramides represented by the general formula (I):



(in the formula, each of R<sup>1</sup> and R<sup>2</sup> represents a straight or branched chain saturated or  
30 unsaturated hydrocarbon group having from 10 to 26 carbon atoms which may be

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substituted with one or more hydroxyl groups) or a substance having its analogous structure, and

(B) one or two or more of cholesterol, cholesterol fatty acid ester, fatty acid, triglyceride, cerebroside and phospholipid.

5           2. The external agent for skin according to claim 1, wherein a blending ratio of the component (A) to component (B) is from 8:2 to 2:8 in weight ratio.

3. The external agent for skin according to claim 1, which further comprises a surfactant.

### 3. Detailed Description of the Invention

#### 10 [Industrial Field of Application]

This invention relates to an external agent for skin, further illustratively to an external agent for skin, which can increase water-retaining capacity of corneum and ameliorate chapped skin.

#### [Related Art]

15           Conventionally, it is known that moisture of the horny layer is important for softening the skin by providing the skin with dampness. In addition, it is considered that said preservation of moisture is due to water-soluble components contained in the horny layer, namely free amino acid, organic acids, urea or inorganic ions, and these substances are used alone or in combination for the purpose of ameliorating or  
20 preventing chapped skin by blending with a medicinal external agent for skin or a cosmetic.

In addition, separately from this, a large number of moisture-retaining substances having high compatibility with water have been developed and used for the same purpose.

#### 25 [Problems that the Invention is to Solve]

However, the action of these moisture-retaining substances when applied to the skin is to provide the horny layer with moisture by presenting on the skin horny layer and the effect is temporary, so that it is not the action to essentially prevent or treat chapped skin by fundamentally ameliorating water-retaining capacity of horny layer.

#### 30 [Means for Solving the Problems]

Under such actual circumstances, the present inventors have conducted intensive studies with the aim of solving the above-mentioned problems and by drawing attention to the lipid between horny cells, and found as a result that a combination of a

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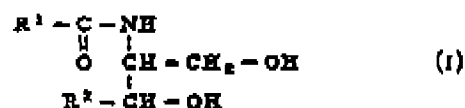
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ceramide or a substance having analogous structure with a lipid existing between  
 honey cells exerts an effect of fundamentally ameliorating water-retaining capacity of  
 horny layer and that the effect can be further improved when a surfactant is  
 concomitantly used in the above-mentioned mixture, thereby resulting in the  
 5 accomplishment of the invention.

That is, the invention provides an external agent for skin, which comprises the  
 following components (A) and (B),

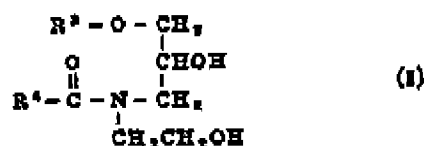
(A) one or two or more of ceramides represented by the general formula (I)



(in the formula, each of  $R^1$  and  $R^2$  represents a straight or branched chain saturated or  
 unsaturated hydrocarbon group having from 10 to 26 carbon atoms which may be  
 substituted with one or more hydroxyl groups) or a substance having its analogous  
 15 structure, and

(B) one or two or more of cholesterol, cholesterol fatty acid ester, fatty acid,  
 triglyceride, cerebroside and phospholipid.

The ceramide (I) to be used in the invention is a conventionally known  
 compound. In addition, the substance having its analogous structure means a lipid  
 20 derivative which has two long chain hydrocarbon groups and has OH group and amido  
 group between them, wherein said molecule can take a conformation on one plane. As  
 such a substance having its analogous structure, for example, an amide derivative  
 represented by the following general formula (II) can be mentioned.



(In the formula,  $R^3$  represents a straight or branched chain saturated or unsaturated  
 hydrocarbon group having from 10 to 26 carbon atoms, and  $R^4$  represents a straight or

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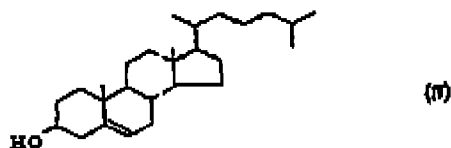
branched chain saturated or unsaturated hydrocarbon group having from 9 to 25 carbon atoms.)

This amide derivative (II) is a novel compound and can be produced in accordance with a conventionally known method [e.g., Polish Journal of Chemistry (Pol. J. Chem.), 52, 1059 (1978), *ibid.*, 52, 1283 (1978), JP-A 54-117421, *ibid.* JP-A-54-144308, *ibid.* JP-A-54-147937]. That is, it can be produced by allowing a compound (III) obtained from a glycidyl ether and ethanolamine in accordance with the reaction scheme shown below to undergo the reaction with a fatty acid methyl ester.

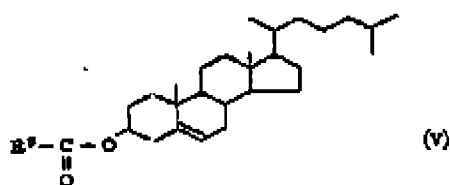


(In the formulae, R<sup>3</sup> and R<sup>4</sup> are as defined in the foregoing.)

As the cholesterol, the substance represented by the following formula (IV) is most desirable, but any derivative can be used with the proviso that the 3-position hydroxyl group is remained.



As the cholesterol fatty acid ester, those which are represented by the formula (V)





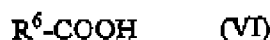
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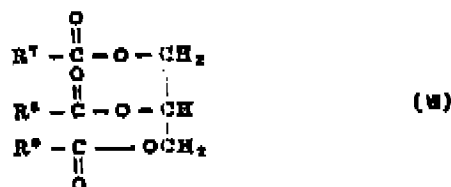
(in the formula,  $R^5$  represents a straight or branched chain saturated or unsaturated hydrocarbon group having from 1 to 25 carbon atoms, which may be substituted with one or more hydroxyl groups) are most desirable; but any derivative can be used with the proviso that the 3-position ester group is remained.

5 As the fatty acid, those which are represented by the general formula(VI)



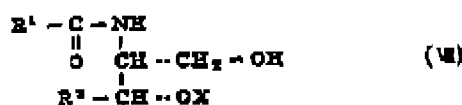
(in the formula,  $R^6$  represents a straight or branched chain saturated or unsaturated hydrocarbon group having from 1 to 25 carbon atoms, which may be substituted with one or more hydroxyl groups) can be used, but a straight chain saturated or unsaturated fatty acid having from 14 to 18 carbon atoms is most suitable.

10 As the triglyceride, those which are represented by the general formula (VII)



(in the formula, each of  $R^7$ ,  $R^8$  and  $R^9$  represents a straight or branched chain saturated or unsaturated hydrocarbon group having from 1 to 25 carbon atoms, which may be substituted with one or more hydroxyl groups) can be used.

15 Cerebroside is a complex lipid in which a sugar is added to the ceramide of the aforementioned formula (I), which is represented by the general formula (VIII)



20

(in the formula, X represents a sugar such as glucose and lactose, and  $R^1$  and  $R^2$  are as defined in the foregoing).

The phospholipid is roughly divided into a glycerin derivative such as glycerophospholipid and a ceramide derivative such as sphingophospholipid, and those which are included in any of them can be used in the invention.

25 It is desirable that the blending ratio of the component (A) to component (B) in the external agent for skin of the invention is from 8:2 to 2:8 in weight ratio. In order

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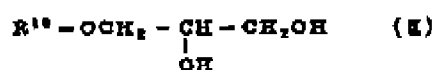
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to blend them, it is desirable that both of them are mixed at the above-mentioned ratio, dissolved with heating once and then cooled, and the product thus prepared into a paste or solid state is added to the other component, but these may be separately added.

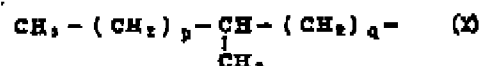
The blending ratio of the component (A) to component (B) in the external agent for skin of the invention is not particularly limited, but in the case of an emulsification type external agent for skin, it is generally from 0.01% by weight to 60% by weight (to be simply shown by % hereinafter), particularly preferably from 0.1% to 30%, based on the total composition, and in the case of an oily external agent for skin, which uses a liquid hydrocarbon such as squalane as the base, it is preferably from 1% to 90%, particularly from 5% to 50%.

As the surfactant which is used in combination in order to further increase the effect of the present invention, any of a nonionic surfactant, an anionic surfactant, and an ampholytic surfactant can be used, and nonionic surfactant is especially preferred among them.

As the nonionic surfactant, there may be mentioned for example a polyoxyethylene alkyl ether, a polyoxyethylene alkyl phenyl ether, a polyoxyethylene fatty acid ester, a sorbitan fatty acid ester, a polyoxyethylene sorbitan fatty acid ester, a fatty acid monoglyceride, a glyceryl ether and the like. Of these, particularly preferred is a glyceryl ether represented by the following general formula (IX)



(in the formula,  $R^{10}$  represents an alkyl group having from 8 to 24 carbon atoms), wherein  $R^{10}$  is represented by the following formula (X)



(in the formula, p is an integer of from 4 to 10 and q is an integer of from 5 to 11, and they have a distribution of  $p + q = 11$  to 17, with  $p = 7$  and  $q = 8$  as the peaks).

The blending amount of the surfactant is preferably from 0.01% to 20%, particularly from 0.1% to 5%, based on the total composition.

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The external agent for skin of the invention is roughly divided into a medicinal external agent for skin and a cosmetic, based on its used embodiments.

As the medicinal external agent for skin, various types of ointments containing an active ingredient can for example be mentioned. The ointments may be either those  
5 which use an oily base as the base or those which use an oil/water or water/oil type emulsion system base as the base. As the oily base, there is no particular limitation, and a plant oil, an animal oil, a synthetic oil, a fatty acid, a natural or synthetic glyceride and the like can for example be mentioned. In addition, as the active ingredient, there is no particular limitation, and for example, an analgesic-anti-inflammatory drug, an  
10 antispasmodic agent, a bactericidal disinfectant, an astringent, a skin softening agent, a hormone drug and the like can be optionally used in response to the necessity.

Also, when used as a cosmetic, in addition to the essential components, those which are generally used as cosmetics components, such as an oil content, a moisture keeping agent, an ultraviolet ray absorbent, alcohols, a chelating agent, a pH adjusting  
15 agent, an antiseptic, a thickener, a pigment, a perfume and the like, can be blended by optionally combining them.

As the cosmetic, there may be mentioned skin cosmetics having various forms such as, for example, a water/oil or oil/water type emulsion cosmetic, a cream, a cosmetic milky lotion, a face lotion, an oily cosmetic, a rouge, a foundation, a skin  
20 cleanser, a hair tonic, a hairdressing, a pilatory, a revitalizing hair tonic and the like.  
[Action]

Though details of the action mechanism of the mixture of the component (A) and component (B) in the external agent for skin of the invention have not been revealed completely, it is considered that this constitutes a lipid bilayer between horny  
25 cells together with water and thereby exerts moisture-keeping function of the horny layer.

[Advantage of the invention]

Since the external agent for skin of the invention contains the mixture of component (A) and component (B) having such an action, it can exert superior  
30 ameliorating and preventive effects on chapped skin.

[Examples]

The following describes the invention with reference to a reference example and examples.

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## Reference Example 1

Synthesis of N-(2-hydroxy-3-hexadecyloxypropyl)-N-2-hydroxyethylhexadecanamide [a case of  $R^3 = C_{16}H_{32}$  and  $R^4 = C_{15}H_{31}$ ] (IIa):

A 5 liter capacity four neck flask equipped with a stirrer, a dropping funnel, a thermometer, a reflux condenser and a nitrogen introducing tube was charged with 1637 g (26.8 mol) of ethanolamine and 327 g (7.11 mol) of ethanol, and while stirring and heating at 80°C under an atmosphere of nitrogen, 400 g (1.34 mol) of hexadecyl glycidyl ether was added dropwise thereto spending 3 hours. After completion of the dropwise addition and further continuation of the stirring with heating for 30 minutes under the same conditions, a distillation device was attached to the flask and the ethanol and unreacted ethanolamine were evaporated under a reduced pressure (from 79°C to 81°C/20 Torr). While stirring with heating at 80°C/20 Torr, 362.3 g of methyl hexadecanoate (1.34 mol) was added dropwise thereto spending 3 hours. After completion of the dropwise addition, the stirring with heating was further carried out for 1 hour under the same conditions, thereby obtaining 801 g of a pale yellow crude product. By recrystallizing this once from hexane and twice from ethanol, 649 g (yield, 81%) of a colorless powder of the compound of interest (IIa) was obtained.

## Example 1

Preparation of a mixture of component (A) and component (B):

The component (IIa) was weighed in a sample bottle with a glass screw cap to a level of 60% by weight, and the cholesterol [formula (IV)] to a level of 40% by weight. The sample bottle was heated to 150°C using a heating block or the like. When the compound (IIa) and cholesterol were completely dissolved by the heating, the heating was stopped and spontaneously cooled in the air to obtain a paste-like mixture.

## Example 2

Using an external agent for skin (product 1 of the invention) prepared by blending vaseline with the mixture obtained in Example 1 in such an amount that the (IIa) became 15% by weight and cholesterol became 10% by weight, another external agent for skin (product 2 of the invention) prepared by blending vaseline with the above-mentioned mixture in such an amount that the (IIa) became 15% by weight and cholesterol became 10% by weight and further blending with 4% by weight of the glyceryl ether [a substance in which  $R^{10}$  in the formula (IX) is that of the formula (X)],

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and vaseline (control), skin conductance and chapped skin were evaluated by the following methods. The results are shown in Table 1.

**[Test methods]**

A total of 10 females of from 20 years to 50 years who caused chapped skin on cheeks in the winter season were used as the persons to be tested, and different samples were applied to the right and left cheeks of each person once a day for 2 weeks. On the next day of the completion of the 2 weeks of application, tests were carried out on the following items.

**(1) Skin conductance**

After washing each person's face with hot water of 37°C and subsequent rest of 20 minutes in a room of 20°C in temperature and 40% in humidity, the moisture content in the horny layer was measured using a skin conductance meter (mfd. by IBS). The skin shows chapped skin when the conductance value is small, and the value of 5 or less reflects a severe chapped skin. When this value is 20 or more on the other hand, the chapped skin can hardly be found.

**(2) Chapped skin score**

Chapped skin was observed with the naked eye and judged by the following criteria. The score was shown by average value  $\pm$  standard deviation.

Score	Judgment of chapped skin
0	Chapped skin was not found
1	Chapped skin was slightly found
2	Chapped skin was found
3	A slightly severe chapped skin was found
4	Severe chapped skin was found

**(Results)**

**Table 1**

	Skin conductance	Chapped skin score
Product 1 of the invention	$30 \pm 4.0$	$1.0 \pm 0.2$
Product 2 of the invention	$45 \pm 5.0$	$0.6 \pm 0.2$
Vaseline	$6 \pm 0.9$	$2.8 \pm 0.7$

**Example 3**

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An oil-in-water type emulsion cosmetic was produced by blending the compound (IIa) with the cholesterol represented by the formula (IV) and stearic acid [ $R^6 = C_{17}H_{33}$  in the formula (VI)] as shown in Table 2, and skin conductance and chapped skin were evaluated using the same methods of Example 2. The results are shown in Table 3.

Table 2

(% by weight)

Emulsion cosmetic	Product 2 of the invention	Comparative product 1
<b>Composition</b>		
Glyceryl ether [ $R^{10}$ in the formula (IX) is that of the formula (X)]	2.0	2.0
Arginine monocetyl phosphate	1.0	1.0
Polyoxyethylene (60) hydrogenated castor oil	1.0	1.0
Octyldodecyl myristate	15.0	15.0
Squalane	15.0	15.0
Stearic acid [ $R^6 = C_{17}H_{33}$ in the formula (VI)]	2.0	-
Compound (IIa)	3.0	-
Cholesterol	5.0	-
Water	balance	balance

Table 3

	Skin conductance	Chapped skin score
Product 2 of the invention	$25 \pm 4.0$	$1.0 \pm 0.2$
Comparative product 1	$6.5 \pm 1.0$	$2.1 \pm 0.5$

10

## Example 4

An oil-in-water type emulsion cosmetic was produced by blending a ceramide represented by the formula (I) [bovine brain ceramide (mfd. by Funakoshi Pharmaceutical Co., Ltd.)], cholesterol isostearate [ $R^5$  in the formula (V) is that of the

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formula (X)], stearic acid [ $R^6 = C_{17}H_{33}$  in the formula (VI)] and 2-ethylhexanoic acid triglyceride [in the formula (VII),  $R^7 = R^8 = R^9 =$   $\begin{array}{c} \text{CH}_3 - (\text{CH}_2)_4 - \text{CH} - \text{CH}_3 \\ | \\ \text{CH}_2 - \text{CH}_3 \end{array}$ ], as shown in Table 4, and skin impedance and chapped skin were evaluated using the same methods of Example 2. The results are shown in Table 5.

5

Table 4			(% by weight)
Composition	Emulsion cosmetic	Product 3 of the invention	Comparative product 2
Glyceryl ether [ $R^{10}$ in the formula (IX) is that of the formula (X)]		2.0	2.0
Arginine monocetyl phosphate		1.0	1.0
Polyoxyethylene (60) hydrogenated castor oil		1.0	1.0
Squalane		20.0	20.0
2-Ethylhexanoic acid triglyceride		1.0	-
Stearic acid		1.0	-
Cholesterol isostearate		0.5	-
Ceramide		5.0	-
Vaseline		4.0	4.0
Water		balance	balance

Table 5

	Skin conductance	Chapped skin score
Product 3 of the invention	$23 \pm 3.5$	$1.1 \pm 0.3$
Comparative product 2	$7.5 \pm 2.0$	$2.3 \pm 0.4$

## 10 Example 5

External agent for skin (oily ointment)

&lt;Composition&gt;

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	(1) Vaseline	30.0 (% by weight)
	(2) Ceramide (1)	10.0
	(3) Cholesterol	3.0
	(4) Cholesterol isostearate	2.0
5	(5) Stearic acid	4.0
	(6) Olive oil	balance for total 100
	(7) <i>L</i> -Menthol	0.3
	(8) camphor	0.3

## &lt;Production method&gt;

10           The components (2) to (6) were mixed and dissolved with heating and added to a preparation separately obtained by mixing the components (1), (7) and (8) and dissolving them with heating, and the resulting mixture was uniformly mixed and then cooled to about room temperature, thereby preparing an oily ointment.

## Example 6

15   Cosmetic (milky lotion)

## &lt;Composition&gt;

## Oil phase components:

	Macadamia nut oil	2.0 (% by weight)
	Squalane	5.0
20	Stearic acid	1.0
	Compound (IIa)	1.0
	Soybean phospholipid	0.5
	Glucocerebroside (bovine brain extract)	0.5
	Sorbitan monostearate	0.5
25	POE (60) hydrogenated castor oil	1.0

## Water phase components:

	Glycerin	1.0
	Propylene glycol	1.0
	Methyl paraben	0.3
30	Perfume	0.1
	Purified water	balance for total 100

## &lt;Production method&gt;



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The oil phase components were mixed, dissolved with heating and then kept at 70°C. The water phase components were also mixed with heating at 70°C in the same manner, and the aforementioned oil phase part was added to the water phase components and emulsified using an emulsifier. The emulsified product was cooled to a final temperature of 30°C using a heat exchanger and filled in a container, thereby preparing a milky lotion.

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